JPTM
Journal of Pathology and Translational Medicine 2021; 55: 236-237
https://doi.org/10.4132/jptm.2021.04.29

EDITORIAL

Prognostic and predictive markers in glioblastoma and ALK overexpression

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Glioblastoma (GBM) is the most common primary malignant brain tumor with a lethal clinical course [1]. Due to recent advances in medical knowledge and treatment modalities, survival of cancer patients has significantly improved. However, prognosis of patients with GBM remains dismal and less than 5% survive more than 5 years despite aggressive surgical resection and concurrent and adjuvant chemoradiation therapy [1-3]. This is the reason why new therapeutic approaches are urgently needed.

In this issue, Elsers et al. [4] reported anaplastic lymphoma kinase (ALK) and telomerase reverse transcriptase (TERT) expression in GBM and their clinical significance. The authors found ALK overexpression significantly correlated with *ALK* gene alterations and TERT expression. In addition, ALK and TERT overexpression and *ALK* gene alterations were associated with poor overall survival (OS) and progression-free survival (PFS), indicating that ALK overexpression could be an additional prognostic marker of GBM.

In GBM patients, age, performance status, extent of surgery, and histologic grade are generally considered prognostic factors [1]. With recent advances in the understanding of molecular pathogenesis of gliomas, certain molecular characteristics of gliomas have been included as prognostic markers [2,5]. Among those molecular alterations, isocitrate dehydrogenase (*IDH*) mutation status is considered as an important prognostic marker for GBM [1,2,5]. *IDH* mutation is typically identified in secondary GBM, which develops from a pre-existing glioma through malignant transformation. Patients with *IDH*-mutant GBM are younger and have a significantly longer survival than patients with *IDH*-wild type GBM [1,2]. IDH is an enzyme involved in the tricarboxylic acid cycle. IDH mutations alter enzymatic activity resulting in production of the oncometabolite, 2-hydroxyglutarate, which can cause tumor-driving epigenetic changes [6]. To date, a target agent for mutant IDH is not available. However, the development of therapies specific for *IDH* mutations will lead to a fundamental change in the treatment of GBM [5].

The blood brain barrier (BBB) is a major obstacle in the development of new drugs for brain tumors. Most chemotherapeutic drugs cannot penetrate the BBB and only a limited number of drugs can be used in treatment of GBM [3,5]. Temozolomide, an alkylating agent that can penetrate the BBB, is currently included in the standard GBM therapy [1,3,5]. Temozolomide induces alkylation or methylation of DNA frequently at the N^7- or O^6-position of guanine residues, which causes cytotoxicity and death of tumor cells. However, tumor cells with O^6-methylguanine-DNA methyltransferase (MGMT) can remove the DNA alkyl group induced by temozolomide, rendering tumor cells resistant to temozolomide [3]. Therefore, MGMT activity status in GBM is considered an important predictive marker of therapeutic effects caused by alkylating agents. Methylation in the promoter region of MGMT can abolish MGMT activity; therefore, analysis of the methylation status in the promoter region of MGMT is currently performed in GBM patients to predict the response to temozolomide [1-3,5].

ALK is a protein with tyrosine kinase activity and encoded by the *ALK* gene located on chromosome 2 [7]. *ALK* gene alterations can promote carcinogenesis [8] and have been reported in various tumors, including anaplastic large cell lymphoma [9], melanoma [8], neuroblastoma [10], and a subset of non-small cell lung carcinoma [11]. The most frequent *ALK*-related genetic aberrations are translocations [12]. In recent studies, ALK overexpression in GBM reportedly ranged from 30%–70% [4,12,13].

Received: April 27, 2021 **Accepted:** April 29, 2021

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pISSN 2383-7837
eISSN 2383-7845

Chiba et al. [14] suggested a possible biological role of ALK in stimulating proliferation and neovascularization in GBM. Dalia et al. [4] showed that ALK overexpression in GBM was significantly associated with proliferation of tumor cells, poor OS, and PFS, indicating a prognostic role in GBM. However, data on the prognostic role of ALK in GBM are very limited and remain controversial [4,12,13]. To properly evaluate the prognostic role of ALK in GBM, further investigative studies with large cohorts are needed.

Chemotherapeutic agents targeting *ALK* genetic alterations (e.g., *EML4-ALK* gene fusion) have been used in clinical practice for treatment of ALK-positive lung cancer and patients showed improved OS and PFS [15]. In GBM, pre-clinical and in vivo studies showed positive outcomes with application of ALK inhibitors in GBM [16-19]. To date, no clinical trials of ALK inhibitors for the treatment of GBM have shown a significant effect on the survival of GBM patients, probably due to low BBB penetration of ALK inhibitors and difficulties in achieving adequate therapeutic concentration in the brain [13,16-19]. However, development of new ALK inhibitors that can penetrate the BBB is ongoing, and if ALK overexpression can predict sensitivity to new ALK inhibitors, ALK overexpression will be an additional important predictive marker in the treatment of GBM.

Ethics Statement

Not applicable.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Code Availability

Not applicable.

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Conflicts of Interest

J.-H.K., a contributing editor of the *Journal of Pathology and Translational Medicine*, was not involved in the editorial evaluation or decision to publish this article.

Funding Statement

No funding to declare.

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